

ORIGINAL RESEARCH



Prescribing trends of inhaler treatments for asthma and chronic obstructive pulmonary disease within a resource-constrained environment in the Scottish national health service: findings and implications

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ABSTRACT

Background: There is an increasing prevalence of asthma and chronic obstructive pulmonary disease (COPD) worldwide, leading to increased inhaler use. However, there are concerns with inhaler compliance resulting in different patented inhalers and longer-acting formulations. As a result, inhalers are now among the highest expenditure items in ambulatory care in Scotland leading to multiple initiatives to keep within budget without compromising care.

Method: This study assesses inhaler utilization and expenditure between 2001 and 2017 alongside health authority initiatives.

Results: There was an increase by 137% in inhaler utilization between 2001 and 2017, and a two-fold increase in expenditure, driven by the increasing use of patented combination inhalers to address concerns. This is very different to the oral markets where expenditure on proton pump inhibitors, statins, and antihypertensives have fallen considerably recently despite increased volumes due to the increasing use of low-cost generics. However, inhaler expenditure has started to fall with an increasing use of lower cost combinations and initiatives to reduce the steroid burden alongside monitoring patient care.

Conclusion: Challenges with using and changing inhalers has meant this market has not followed other high-volume drug classes following patent loss. This is starting to change, with the situation monitored to enhance efficient prescribing alongside continued good quality care.

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1. Introduction

There is an increasing prevalence of asthma and chronic obstructive pulmonary diseases (COPD) worldwide, with asthma now one of the most common non-communicable chronic diseases [1]. Globally asthma affects 334 million people and is rising particularly in developing countries [1,2], which negatively impacts on their quality of life and survival [1]. In the UK, 5.4 million people are currently receiving treatment for asthma, and in Scotland, one in 14 of the population currently receives treatment for asthma. However, prevalence rates have plateaued in recent years [3]. Globally, it is estimated there were 251 million cases of COPD in 2016, with the number of cases likely to rise with increasing aging populations and more people smoking [4,5]. By 2030, COPD will be one of the top ten causes of death worldwide without improvements in prevention and management [2,6,7]. It is estimated that approximately 3 million people in the UK currently have COPD [8], with prevalence rates increased by 9% between 2008 and 2012 [5].

Concerns with the extent of asthma and COPD among countries, with their associated impact on morbidity and mortality, have resulted in efforts globally, regionally, and nationally to improve patient care, which include guideline production and quality improvement strategies [1,9–13]. In the UK, the Quality and Outcomes Framework (QoF) includes targets to measure, monitor and improve the identification and management of patients with asthma and COPD [14,15]. In Scotland, there has also been the Scottish Intercollegiate Guidelines Network (SIGN) guidelines for asthma [16] as well as the publication of the Clinical Standards guidance for patients with COPD, recognizing that during the last decade COPD was the only major cause of death increasing in Scotland [17]. There was a further update on best practice guidance for COPD in 2017, with COPD accounting for 122,000 emergency bed days annually in Scotland with an average inpatient stay costing GB£3000 per patient [8].

There have also been national respiratory prescribing strategies in Scotland to promote appropriate, evidence-based, and cost-effective prescribing of treatments for asthma and COPD,

predominantly inhalers, as NHS Scotland currently spends over GB £125 million per year on respiratory medicines [18]. Typically, in patients with asthma, inhaled corticosteroids (ICS) are first-line treatment followed by combined long-acting β -agonists (LABAs)/ICS for more severe asthma, with short acting β -agonists (SABAs) used as rescue 'reliever' therapy [1,13,16,19]. Tiotropium is also now being prescribed for patients with asthma. In COPD, both LABAs and long-acting muscarinic antagonists (LAMAs) have been used alone or in combination, with LAMA use growing with studies showing a greater effect in reducing exacerbations and hospitalizations [20,21]. The use of LABA/ICS inhalers for COPD has also grown in recent years following a number of studies [22–27]. However, there are now concerns with the increased risk of serious pneumonia [27]. As a result, more recent guidance suggests that combination LABA/ICS should only principally be prescribed in COPD patients with asthma-like symptoms with exacerbations in view of potential adverse effects [12,21]. It can be difficult though to assess differences in outcomes between the different combination formulations and inhaler types [28–32]; consequently, the choice of inhaler device and ease of use do play an appreciable role in the choice of device prescribed with poor inhaler technique known to compromise care [33–37].

Scrutiny regarding the quality and costs of prescribing for patients with respiratory diseases has grown in recent years with, as mentioned, NHS Scotland currently spending over GB £125 million per year on respiratory medicines [18]. This makes the inhalers the second highest medicine category in Scotland [18]. Increasing expenditure on inhalers has been driven by the availability of new patented devices to address concerns with their effectiveness and adherence despite the patents on many of the active ingredients expiring, with poor inhaler technique and adherence known to considerably increase the costs of asthma and COPD [38]. Concerns with the overall cost of inhalers in Scotland, but mindful of the need to ensure good quality care, have also resulted in a number of initiatives to improve the prescribing of inhalers to patients with asthma and COPD to help ensure the optimal use of available resources [19,20,39–41]. This is because both asthma and COPD can be lifelong conditions once diagnosed, requiring regular monitoring and review of current therapeutic strategies, presenting a considerable challenge in terms of the budget implications with different treatment approaches whilst remaining firmly focused on improving clinical outcomes along with patient safety. This patient focus has meant that inhalers are typically prescribed by their brand name with the potential exception of ABA MDIs. This is because pharmacists in Scotland are not allowed to substitute a branded product with a generic [42].

It is envisaged that the inhaler market will be very different from the typical oral markets where considerable savings can be made following generic availability as seen with the Proton Pump Inhibitors (PPIs), statins, and antihypertensives [42–44]. Firstly, there are known concerns with how well or not patients have used their inhalers in the past resulting in activities including patient education and actively involving patients with inhaler choices to help address this [33,45–50]. As mentioned, concerns with adherence and poor technique have also resulted in new inhaler devices being developed as well as new medicines

being developed including LABAs and LAMAs as well as longer acting steroids. Secondly, there are concerns for subsequent patient care if patients are switched between inhaler types without their consent, knowledge or training [49,51,52]. Lastly, there are concerns with switching between different inhalers with the same active ingredients in view of potential issues such as appropriate dosing and adherence [41].

We are also aware that alternatives to Seretide® and Symbicort® are typically priced at a discount of only 20% to 30% below originator prices rather than the 85% to 95% reductions seen for generic PPIs, statins and selective serotonin reuptake inhibitors (SSRIs) versus pre-patent loss prices [42,53,54]. As a result, expenditure on LABA/ICS and LAMA inhalers has grown in recent years to become the highest of any medicine type in Scotland. To help address this, new lower cost LABA/ICS inhalers, e.g. Fostair® (beclomethasone/formoterol) and Revlar® (fluticasone furoate/vilanterol) have recently been promoted by the Health Boards in Scotland as the preferred first and second line choices [39–41]. There were concerns initially that these new inhalers did not have the same dose range as Seretide® and Symbicort®, which made it difficult to titrate care. In addition at the time of their launch, there were ongoing initiatives with Health Boards to encourage physicians to step down inhaler doses particularly the steroid burden in line with current guidance (BTS/SIGN). Consequently, it was perceived as challenging to initiate this steroid dose change as well as switch patients between different inhaler types. There was also a need for all key stakeholders to become comfortable with Fostair® or Revlar®, which resulted in a gradual uptake initially as well as acknowledging the resource implications with patient training [50]. There have also been concerns with the licensed indications of these alternatives versus Seretide® and Symbicort® when initially available.

Consequently, there is a need to investigate the effects of these multiple national and regional activities on the utilization and expenditure patterns of the different inhalers used in the management of asthma and COPD in Scotland. The findings will be used as a basis for reviewing and debating potential future policies to improve the quality and efficiency of prescribing for both asthma and COPD given concerns with expenditure within resource constrained environments but mindful of the need to continue to ensure good quality care. We are aware that there have been publications assessing the impact and factors associated with poor inhalation techniques as well as different educational policies to address concerns [34,37,38,49,50]. However, we are not aware of any study that has assessed the influence of multiple international, national and regional policies on inhaler utilization and expenditure patterns during the past seventeen years to provide future guidance.

2. Methodology

Utilization and prescribing patterns of inhalers in Scotland were assessed using the prescription costs analysis (PCA) data compiled by the Information Services Division (ISD) of NHS Scotland from 2001 to 2017 [55]. This is an open source data set collecting data on the utilization and expenditure of medicines dispensed in community pharmacies in Scotland. NHS Scotland is

a universal healthcare system serving the entire Scottish population, with currently no co-payment for medicines in Scotland. The information from the PCA included: the generic (INN) name, commercial name(s), formulation(s), drug strength(s), number of dispensed units, cost per unit and total gross expenditure. All costs are depicted in Great Britain pounds (GB£s). No attempt was made to allow for inflation as typically medicine costs in Scotland appreciably fall once generics become available and prices for originators are typically fixed [42,43].

Data on inhaled medicines from the following classes as defined by the British National Formulary [56] were incorporated into the study: SABAs, SAMAs (short acting muscarinic antagonists), LABAs, LAMAs, mast cell stabilisers, ICS as well as combinations such as SABA/SAMA, LAMA/LABA, ICS/LABA and ICS/SABA. We concentrated on guideline-recommended inhalers for patients with asthma and COPD, acknowledging that in patients with asthma a LABA is typically not prescribed without an ICS and in COPD, an ICS is not licensed without a LABA. Consequently, both are typically given in combination.

Between 2001 and 2017, 144 individual inhalers were included covering both originators, alternatives to originators and generics. In terms of active ingredients, the following were available during the study period although a number of these inhaler types are no longer available: five SABAs (salbutamol, terbutaline sulphate, fenoterol hydrobromide, orciprenaline sulphate and reproterol hydrochloride), two SAMAs (ipratropium bromide and oxitropium bromide), three LABAs (salmeterol, formoterol fumarate and olodaterol), three LAMAs (tiotropium, aclidinium bromide and umecclidinium bromide), two mast cell stabilisers (nedocromil sodium and sodium cromoglicate), five ICS (budesonide, beclometasone dipropionate, ciclesonide, fluticasone propionate and mometasone furoate), one SABA/SAMA (salbutamol with ipratropium), three LAMA/LABA (umecclidinium bromide with vilanterol trifenate, aclidinium bromide with formoterol fumarate and tiotropium with olodaterol), five ICS/LABA (salmeterol with fluticasone propionate, budesonide with formoterol fumarate, fluticasone furoate with vilanterol, fluticasone propionate with formoterol fumarate and beclometasone dipropionate with formoterol fumarate) and one ICS SABA (beclometasone dipropionate with salbutamol).

From the PCA data, the units dispensed (typically an inhaler) and associated expenditure patterns were calculated for each drug class. When presenting and assessing utilization data, NHS Scotland regularly uses defined daily doses (DDDs) as well as DIDs (DDDs/1000 inhabitants/day) in line with international guidelines [57–59]. However, for the purpose of this study, items dispensed in community pharmacies, which were typically an inhaler, were used in order to track actual prescriptions to assess the influence of guidelines/legislation, e.g. encouraging the prescription of combined LABA/ICS inhalers. In addition, DDDs are not available for combination inhalers [58]. We used a segmented regression analysis to assess the influence of the various initiatives to enhance the prescribing of newer formulations of ICS/LABAs such as Fostair® or Revlar® as they became increasingly endorsed by the Health Boards. We also plotted changes in the utilization and expenditure patterns for the various inhaler ingredients over time.

These multiple initiatives undertaken by Scottish Health Boards and NHS Scotland to influence physician prescribing were consolidated using the 4E methodology in line with previous studies: Education (guidelines and academic detailing interventions), Engineering (organizational/managerial interventions, e.g. prescribing indicators), Economics (financial incentives for prescribing) and Enforcement (enforced regulations by health authorities – although not generally applying to Scotland) [42–44,60–63]. Examples of enforcement including compulsory INN prescribing in Lithuania, compulsory generic substitution in Sweden and restrictions on the prescribing of patented statins in Austria and Finland [64–67]. However, such activities are difficult in Scotland [42].

No ethical approval was needed as only publicly sourced aggregated drug utilization, and expenditure data was used for analysis. No patient level data were accessed.

3. Results

Table 1A in the Appendix summarises the various drug classes, the name of the first in class, as well as the number of strengths and formulations available during the course of the study.

3.1. Demand-side initiatives

Table 1 summarises some of the many NHS Scotland and Health Board activities during the study period to influence the utilization and expenditure of inhalers for asthma and COPD in Scotland. This includes safety concerns if patients are inappropriately prescribed high dose inhaled steroids as well as concerns with the increasing costs of Seretide® [8,16,17,39,40,57,59,68–79].

3.2. Utilization and expenditure patterns

Both utilization and expenditure on inhalers steadily increased between 2001 and 2017. Total items dispensed increased from 3.45 million units in 2001 to 4.72 million units in 2017 with expenditure increasing from GB£48.64 million in 2001 to GB£95.17 million in 2017, respectively (Figures 1 and 2). This represents a 137.1% increase in items dispensed and 195.7% increase in total expenditure during the study period.

More specifically, there was a steady increase in dispensed items for LABAs/ICS during the study period, with the use of SABAs continually increasing each year as well but at a lower rate (Figure 1). Alongside this, there was a steady decline in the use of single-agent ICS inhalers and single-agent LABA inhalers, reflecting recommended treatment approaches (Table 1). There has also been an increase in the prescribing of LAMAs following their availability and more recently LAMA/LABA combinations but from a low base. Conversely, a steady decline in the use of SABAs and SAMAs in combination (Figure 1) and limited use throughout of ICS/SABA combinations. The decline in the use of ICS/SABA combinations reflects their withdrawal from the market place.

During this period, there was also a steady increase in expenditure on combination LABA/ICS until recently (Figure 2), as well as

Table 1. Summary of various initiatives, guidelines, and policies introduced regionally and nationally in Scotland between 2001 and 2017.

Measure	Year	National or Regional	Initiative
Education	2001	National	MHRA warning of systemic side effects following high dose fluticasone
	2003–2016	National	SIGN guidance on asthma – first published 2003 and updated 2016
	2003 and updated	Regional GGC	Guideline on the management of Asthma
	2004 and updated	Regional (GGC)	Guideline on the management of COPD
	2006	Regional (GGC)	ICS formulary recommendations updated emphasizing potency differences of CFC-free beclomethasone inhalers
	2008 and updated	Regional (Forth Valley) and Lothian	Guideline on the management of COPD as well as a guide to support changes to CFC free inhaled corticosteroid devices
	2010	National	Guidance on clinical standards for patients with COPD
	2009–2014	Regional (Lothian)	Lothian COPD Guidelines, updated in 2010, 2014 and recently. In 2011, Lothian introduce Fostair® onto the formulary and provided guidance when stepping up asthmatic patients from Clenil® or Qvar® (two formulations of beclomethasone with different particle sizes)
	2013	Regional (GGC)	Respiratory Inhaler Identification Guide as well as revised COPD Guideline
	2014–2016	National	Respiratory Prescribing Strategy 2014 to 2016 and updated for 2018 to 2021
Engineering	2014	Regional (Tayside)	COPD Guidelines
	2016	Regional (GGC)	• Fostair® and Relvar® as combination ICS/LABA for asthma and COPD with Seretide® and Symbicort® no longer recommended
	2017	National	• LAMAs: First choice: umecclidinium bromide and second choice: aclidinium bromide. In 2018, this changed to Seebri® (Glycopyrronium)
	2017/2018	Regional (GGC)	Prescribing guidance for asthma including Fostair® and Relvar® as preferred ICS/LABA combination
	2017/2018	Regional (Lothian and other Boards)	COPD Best Practice Guidance
	2017	Regional (GGC)	Braltus® – (tiotropium) – accepted onto the formulary
	2017/2018	Regional (Lothian and other Boards)	Following GOLD guidance – Health Boards producing advice on stepping patients with COPD off ICS/LABA combinations
	2003	National (Audit Scotland)	Consider substituting salbutamol dry powder automated inhalers with standard inhalers for patients with asthma
	2009	National	Better Health, Better Care and HEAT Targets:
	2009	Regional (GGC)	• Establish respiratory Managed Clinical/Care Networks including working together to improve the management of asthma in children and young people
Economics	2009	Regional (GGC)	• Achieve agreed reductions in the rates of hospital admissions and bed days of patients with COPD and Asthma from 2006/7 to 2010/11
	2010	Regional (Tayside)	Practice pharmacist medication reviews for patients with COPD
	2010	Regional (GGC)	2010/11 Seretide® Cost-minimization initiative
	2012	National (Therapeutic Indicators)	Fluticasone inhalers cost-minimization initiative
	2013	National (Audit Scotland)	The proportion of high dose ICS prescribed of all ICS inhalers prescribed for asthma or chronic obstructive pulmonary disease
	2013–2017	National (Therapeutic indicators – NTIs)	Consider substituting salbutamol dry powder automated inhalers with standard inhalers for patients with asthma
	2016	National	• The proportion of high strength corticosteroid inhalers prescribed compared with the total amount of inhalers, with typically high dose ICS under the care of a pediatrician. This changed in 2016 to:
	2016	Audit Scotland	o High dose corticosteroid inhalers as a percentage of all corticosteroid inhalers.
	2016	National and Regional	o Medium and high strength corticosteroid inhalers prescribed to children.
	2014	Lothian	• Fostair® excluded from 2016 BTS/SIGN guidance with Health Boards uncertain whether it should be counted as high strength or not. As a result, the NTIs in Scotland were reported with or without Fostair® as a high strength ICS
Enforcement	2014–2016	National	• It is recommended that patients on high dose ICS carry a steroid card
	2016	Audit Scotland	Respiratory Prescribing Strategy 2014 to 2016 and updated for 2018 to 2021
	2016	National and Regional	Highlighting that inhalers containing salmeterol with fluticasone propionate have the highest total cost in ambulatory care in Scotland (£35.5 million)
	2014	Lothian	Patients receiving ICS to be reviewed every three months to facilitate stepping down and reduce excessive high dose steroid prescribing
	2014	Regional (Forth Valley)	Lothian respiratory MCN Action Plan 2014 to 2015 launched building on earlier plans
	2014	Regional (GGC)	Respiratory MCN updated the FV formulary choices for Asthma and COPD
	2017	Regional (Lothian and other Health Boards)	Triple therapy inhalers for COPD added to formulary
	2017/2018	Regional (Lothian and other Health Boards)	Following GOLD guidance – Advice produced locally including how to consider withdrawing ICS from some COPD patients
	2018	Regional (GGC)	Moving patients with COPD to triple therapy
	2002	National	Tiotropium approved for general use by the Scottish Medicines Consortium
Enforcement	2014–2017	National	Local Enhanced Service (LES) for prescribing outlined where practices are paid for targets achieved
	2018–2019	Regional (GGC)	Prescribing Initiative for combination inhalers
	2006–2009	National	Withdrawal of CFC containing metered-dose inhalers

NB: MCN = Managed Clinical Network. Health Authorities in Scotland are called Health Boards.

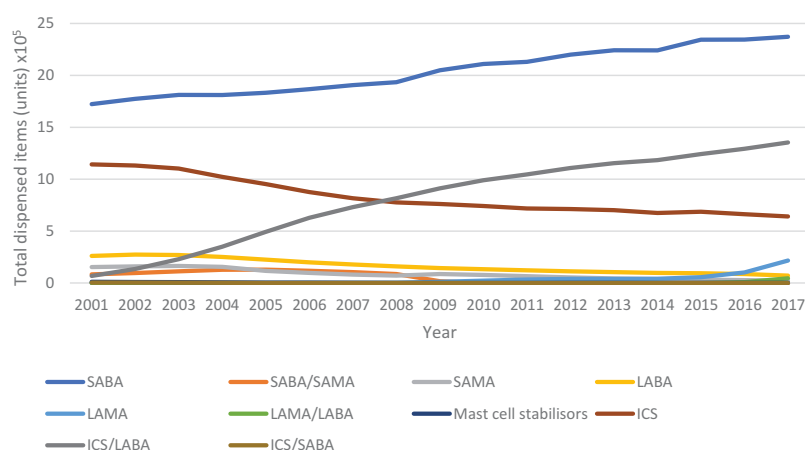


Figure 1. Utilization (items dispensed of the different inhaler types in Scotland by drug class between 2001 and 2017 (Source ISD Scotland – [55]).

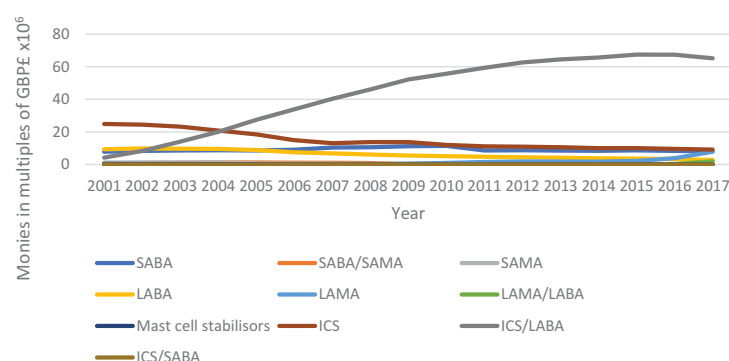


Figure 2. Expenditure (GB£) on different inhaler types in Scotland between 2001 and 2017 (Source ISD Scotland – [55]).

increased expenditure on LAMAs. Expenditure on these combination inhalers and LAMAs has driven the increase in expenditure on inhalers in Scotland in recent years. Overall, expenditure on these combination inhalers and LAMAs rose from 8.6% of total inhaler expenditure in 2001, to 32.4% in 2004, to 62.8% in 2009 soon after the launch of LAMAs, and 75.4% in 2017.

There has been a steady decline in the utilization and expenditure of originator LABAs/ICS in recent years following the availability and endorsement of alternative inhalers, e.g. Fostair® and Relvar® (Table 1) (Figures 3 and 4). It is envisaged that the utilization of LABA/ICS combinations will plateau or even fall following the change in GOLD guidance (Table 1). The change in the prescribing of Seretide® and Symbicort® to alternative inhalers such as Fostair® and Relvar® has been significant, i.e. $p < 0.001$.

As seen (Figure 4), this change in LABA/ICS utilization patterns (Figure 3) has resulted in their expenditure falling in recent years with growing use of lower priced alternative inhalers (Fostair® and Relvar®). In addition, initiatives to encourage lower strength steroid inhalers in recent years (Table 1) also facilitated in reduced expenditures. Fostair® and Relvar® now account for 24.5% of total expenditure on LABAs/ICS (2017) in Scotland and growing rapidly (6.8% in 2015 and 13.2% in 2016). This reduction in expenditure of Seretide® and Symbicort® with a corresponding increase in expenditure

of alternative LABA/ICS inhalers such as Fostair® and Relvar® have also been significant ($p < 0.001$).

4. Discussion

The utilization patterns of the different inhaler types for patients with asthma and COPD (Figure 1) are in line with national and regional guidance (Table 1) with inhaled ICS used initially in patients with asthma, with combination ICS/LABAs used for maintenance and further treatments added when required. In patients with COPD, LAMAs are increasingly recommended alongside LABA/LAMA combinations as well as triple therapy with increasing fears about using combination LABAs/ICSs unless patients also have asthmatic features (Table 1). The effect of these guidelines can also be seen with limited utilizing of mast cell stabilizers (Figure 1) in line with their exclusion.

The growth in the utilization of inhalers in Scotland is also in line with increasing prevalence rates especially for COPD [5]. The higher utilization of Seretide® over Symbicort® (Figure 3) may be due to the preference of clinicians as opposed to any appreciable differences in clinical outcomes. This may have arisen because GSK is a long-standing company in this area in the UK, initially through Allen and Hanburys. However, further research is needed before any definitive statements can be made.

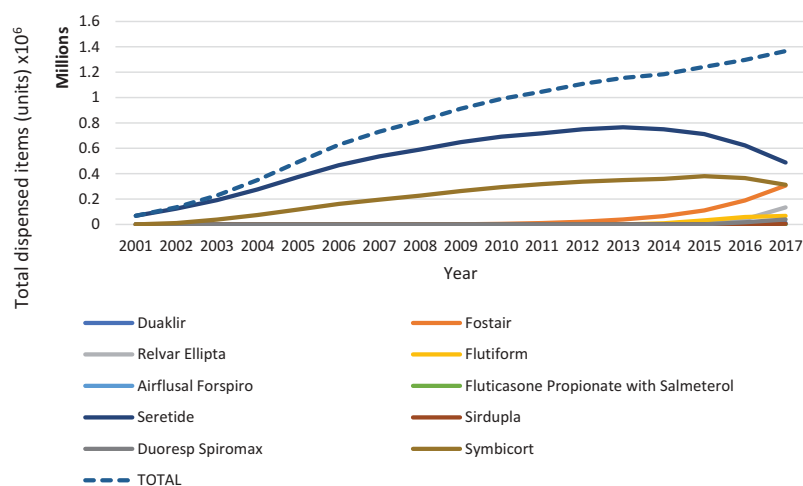


Figure 3. Total utilization of LABA/ICS inhalers in Scotland between 2001 and 2017 (Source ISD Scotland – [55]).

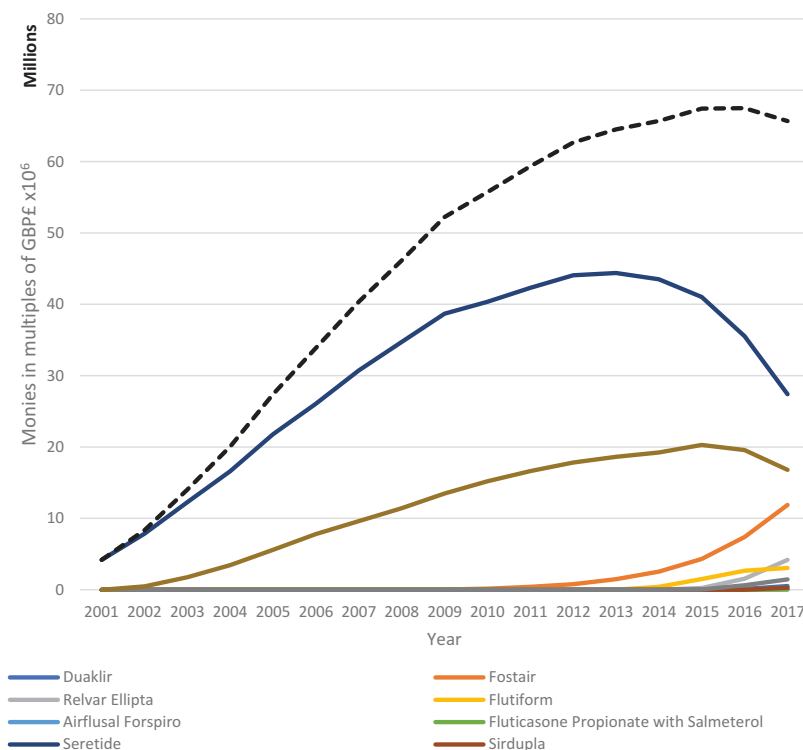


Figure 4. Total expenditure (GB£) on LABA/ICS inhalers in Scotland between 2001 and 2017 (Source ISD Scotland – [55]).

Inhaler expenditure increased from GB£48.64 million in 2001 to GB£85.91 million in 2010 and to GB £95.17 million in 2017 (Figure 2), enhanced by the prescribing of Seretide®, Symbicort®, and Spiriva®. Traditionally, as mentioned, the focus of managing patients with asthma and COPD in Scotland has been on educating patients to improve their inhaler technique and adherence rates [33,38]. In addition, making sure optimal doses of ICS are given, which in recent years has meant a reduction in the steroid burden (Table 1). However, the high and growing expenditure on originator ICS/LABAs up to 2010 resulted in Health Board initiatives to increase the use of alternative inhalers (Table 1 – Figure 3).

Concurrent with this, there has been ongoing monitoring of patients to ensure care is not compromised. In addition, regular monitoring of inhaler prices especially when originator companies lower their prices to help retain or slow down their decline in utilization. The increasing use of alternative inhalers, coupled with initiatives to reduce the steroid burden and associated costs, appear to have moderated the growth in overall inhaler expenditure (Figures 2 and 4) for now at least.

The usage and expenditure patterns for respiratory inhalers (Figures 1 and 2) did not follow the same patterns as seen with other common classes of medicines prescribed in ambulatory care in Scotland when medicines lose their patent such as

antihypertensive medicines, PPIs, SSRIs and statins [42–44,53]. Consequently, we did not see appreciable reductions in inhaler expenditures as the constituent medicines lost their patents with the launch of newer inhalers replacing the older ones (Appendix 1A) and, as mentioned, price reductions with newer inhalers being more modest [42,43]. As a result, expenditure on inhalers increased by 195.7% between 2001 and 2017 with utilization only increasing by 137.1%. This increase in expenditure reflects the promotion of ICS/LABA combination therapies until recently for patients with COPD (Table 1), the more modest price reductions of Fostair® and Relvar® compared to Symbicort® and Seretide®, as well as the challenges of treating patients with respiratory diseases including concerns with regularly switching patients between inhalers particularly if there are color changes [80]. This was an issue with Relvar® limiting initially its use in practice. Concerns with switching patients to different inhalers whose condition is relatively controlled have the potential for increasing exacerbations. The extent though of this increased risk is under debate with some authors suggesting that any risk is so high that any switching of inhalers is unwarranted and could be costly [38,52,81]; however, others have suggested there is no real risk and patient care and clinical outcomes are of the same standard when using alternative inhalers [82].

Overall, constant monitoring of patients coupled with education on inhaler techniques as well as other initiatives helps ensure patients in Scotland are treated as well as possible within available resources. Such approaches are facilitated by the fact that community pharmacists cannot substitute branded medicines in the UK [42]. This situation is being closely monitored though in view of the recognized need to continue to offer high standards of care to patients with asthma and COPD in Scotland but mindful of the current high expenditure on inhalers. There are also concerns that the expiry dates of the newer inhalers are being reduced once opened, and this situation will also be closely monitored. One potential approach is that all key stakeholder groups become used to a more limited number of inhalers so adherence and outcomes can be maximized. However, the range has to be sufficient to cover patient needs.

4.1. Limitations

We are aware it cannot be categorically assumed that all inhalers in this study are being prescribed for the treatment of asthma or COPD. However, it is believed that the prescribing of these inhalers for other indications is currently very limited. There was also an inability to assess adherence to the different inhalers including the newer combination inhalers, or their impact on patient outcomes, using the PCA data. In addition, prescribing and dispensing data are not always equal to each other. Despite these limitations, we believe our findings are robust providing direction for the future.

5. Expert opinion

There has been considerable growth in the utilisation of combination inhalers involving long acting β -agonists (LABAs) and

inhaled corticosteroids in Scotland in recent years to treat an increasing number of patients with asthma and COPD in line with current guidelines. Different patented inhalers have been made available over the years to help address concerns with compliance with inhalers with patients typically involved in their selection. However, the increasing prevalence of respiratory diseases, coupled with patent protection for different inhaler types, has resulted in inhalers becoming the second highest category for drug expenditure in Scotland in recent years. This has focused attention on newer lower cost combination inhalers. There were initially concerns that the newer inhalers did not have the same dosage range as Seretide® and Symbicort®, and it took time for all key stakeholder groups to become comfortable with their use. This resulted in a slower uptake initially to ensure patient care was not compromised. This has started to change with more rapid growth rates in recent years. It is likely the use of lower cost alternative combination inhalers will continue to grow to help conserve resources. This together with initiatives to reduce the steroid burden in patients has resulted in expenditure on inhalers stabilising in recent years. This is likely to continue with recent guidelines advocating caution in the use of combination inhalers in patients with COPD counteracting any increased utilisation from any future growth in prevalence rates. Overall, the inhaler market is very different to the oral market where there have been substantial reductions in expenditure in classes following the availability of low cost generics. This is likely to remain with more modest price reductions envisaged for the newer alternative combination inhalers versus the originators.

6. Conclusion

We believe this is the first comprehensive study in the UK and across Europe to evaluate the influence of multiple international, national and regional initiatives on the utilization and expenditure patterns of different inhalers used for the management of asthma and COPD in recent years.

Overall, the utilization and expenditure patterns for inhalers used for the treatment of asthma and COPD in Scotland have not experienced the same trends as other high volume classes in ambulatory care in terms of decreasing expenditure despite increasing utilization once standard medicines in the class lose their patent. This is due to a number of factors including the need to have a range of inhalers to choose from, the patent situation associated with new devices and new formulations, concerns with switching, and more modest price reductions with the newer alternative combination inhalers compared to their originators.

For any health service with finite resources, cost is a key consideration as seen recently regarding Scotland's Health Board advice on Fostair® and Relvar®. However, improved patient care and safety is paramount for patients with asthma and COPD as seen by the various international, national and regional initiatives and guidelines which have appreciably influenced prescribing patterns in Scotland, most notably resulting in the increasing use of LABA/ICS inhalers (until recently) and reduced prescribing of single agent ICS and LABA inhalers. However, further research is needed to fully assess the cost-effectiveness of the different approaches in Scotland including educational and other

initiatives to enhance patient adherence and improve future care efficiently. Ideally, all key stakeholder groups should work together to rationalize the inhaler choices available and improve familiarity to help conserve costs within a constrained resource environment. These are projects for the future.

Key issues

- There is increasing prevalence of asthma and COPD across countries, with both priority areas in Scotland
- There has been the continual launch of new patented inhalers to help address concerns with adherence to inhalers. This coupled with increased prevalence rates has meant a two-fold increase in inhaler expenditure in Scotland between 2001 and 2017
- As a result, NHS Scotland spends over GB£125 million per year on respiratory medicines, with expenditure on LABA/ICS and LAMA inhalers becoming the highest of any medicine type in Scotland
- However, concerns with the availability of the full dose range of alternative combination inhalers to Seretide® over Symbicort®, coupled with the need to be cautious initially as health-care professionals and patients became more familiar with alternative inhalers and their more modest price reductions have resulted in total expenditure in inhalers plateauing in recent years compared with the appreciable reductions in expenditure on oral medicines once generics become available. Recent initiatives to reduce the steroid burden have also impacted on expenditures
- There is ongoing monitoring of patients to ensure care is not compromised with the increasing use of alternative combination inhalers, and this will continue
- The utilization of combination ICS/LABAs in COPD will be affected by recent concerns with their safety

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Appendix

Table 1A. Summary of different inhaler drug classes (Source ISD Scotland – [55]).

Drug Class	Active Ingredient	Originator	Number of strengths and formulations (2001 vs. 2017)
SABA	Salbutamol	Ventolin®	19–15
	Terbutaline Sulfate	Bricanyl®	6–2
	Fenoterol Hydrobromide	Duovent®	6–0
	Orciprenaline Sulfate	Alupent®	4–0
	Reproterol Hydrochloride	Bronchodil®	2–0
SAMA	Ipratropium Bromide	Atrovent®	6–2
	Oxitropium Bromide	Oxivent®	4–0
LAMA	Tiotropium	Spiriva Respimat®	0–2
	Aclidinium Bromide	Eklira Genuair®	0–2
	Umeclidinium Bromide	Incruse Ellipta®	0–2
Mast Cell Stabilizers	Nedocromil Sodium	Tilade®	4–2
	Sodium Cromoglicate	Intal®	8–2
ICS	Budesonide	Pulmicort®	10–14
	Beclometasone Dipropionate	Becotide®	42–19
	Ciclesonide	Alvesco®	6
	Fluticasone Propionate	Flixotide®	22–14
	Mometasone Furoate	Asmanex®	0–8
SABA/SAMA	Salbutamol/Ipratropium	Combivent®	1–0
LAMA/LABA	Umeclidinium Bromide/Vilanterol	Anoro®	0–0
	Tiotropium/Olodaterol	Spiolto Respimat®	0–1
ICS/LABA	Salmeterol/Fluticasone Propionate	Seretide®	0–11
	Budesonide/Formoterol Fumarate	Symbicort®	0–6
	Fluticasone Furoate/Vilanterol	Relvar Ellipta®	0–2
	Fluticasone Propionate/Formoterol Fumarate	Flutiform®	0–3
	Beclometasone Dipropionate/Formoterol Fumarate	Fostair®	0–4
ICS/SABA	Beclometasone Dipropionate/Salbutamol	Ventide®	1–0

NB: There have been changes in the availability of different inhaler types during the course of the study as well as CFC and CFC-inhaler types. Some formulations were also never licensed in the UK but may have had limited use.